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10/553,629	07/20/2006	Svenn Kluver Jepsen	15041.10USW1	6061

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
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02/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,629	JEPSEN, SVENN KLUVER	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7 and 9-33* is/are pending in the application.

4a) Of the above claim(s) *12-20,22-25,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-7, 9-11, 21, 26-30, 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 10/16/09 are acknowledged.

2. Claims 2-5 and 8 were cancelled. Claims 12-20, 22-25 and 31-32 were withdrawn. Claims 1, 7 and 9 were amended. New claim 33 was added.

3. Claims 1, 6-7, 9-11, 21, 26-30, and 33 are included in the prosecution.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 10/16/09 is acknowledged. Please note that the Murata et al. reference (NPL: Murata et al., Integrated Essentials, 5th ed., 1997, 127-129, 140-143) was not in English and was not considered. See attached copy of PTO-1449.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 7, 9-11, 21, 26, 29, and 30 **remain** rejected and **new claim 33** is rejected under 35 U.S.C. 103(a) as being unpatentable over Halskov (WO 81/02671) in view of Valducci (US 2002/0034541 A1).

The claimed invention is an oral pharmaceutical formulation in the form of a coated granulate in a sachet, wherein the coated granulate comprises: a pharmaceutically acceptable binder, from 92 to 98% by weight of mesalazine or a pharmaceutically acceptable salt thereof, and an amount of coating adjusted to the specific surface area of the granulate to provide the in vitro release characteristics of: a) 5-25% of the total amount of mesalazine or pharmaceutically acceptable salt thereof in the formulation is released after 15 min; b) 30-70% of the total amount of mesalazine or pharmaceutically acceptable salt thereof in the formulation is released after 90 min; and c) 75-100% of the total amount of mesalazine or pharmaceutically acceptable salt thereof in the formulation is released after 240 min; when measured in a model system using a USP Paddle System 2 operated at 37°C with stirring at 100 rpm.

Halskov teaches a granulate comprising 250g of 5-ASA (5-aminosalicylic acid) with 25g of polyvinylpyrrolidone dissolved in isopropanol (Page 11, lines 15-18). “Upon evaporation of the isopropanol the resulting dry granulate is sprayed with 45g of ethyl cellulose dissolved in acetone (3:97 w/w) resulting in granulate particles individually coated with ethyl cellulose upon evaporation of the acetone" (Page 11, lines 18-23). The calculated amount of 5-ASA (or mesalazine) is 250g/275g = 91% of 5-ASA per granulate. The calculated amount of 5-ASA (or mesalazine) based on the weight of the coated granulate is: 250g/320g = 78%.

Halskov does not expressly teach a sachet comprising the coated granulate of 5-ASA (or mesalazine) or adjusting the amount of coating to the specific surface area of

the granulate to achieve specific in vitro release characteristics when measured in a model system using a USP Paddle System 2 operated at 37ºC with stirring at 100 rpm.

Valducci teaches sachets and dispensers for granules or microgranules containing a mesalazine dosage ranging from 100 and 3000mg (Page 3, [0045]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a granulate comprising 5-ASA (or mesalazine), polyvinylpyrrolidone, and coat the granulate with ethyl cellulose, as taught by Halskov, place the granules of mesalazine in sachets, as taught by Valducci, measure the in vitro release profile of the mesalazine, as established in the standard USP protocol during the process of routine experimentation, and produce the instant invention.

One of ordinary skill in the art would do this because sachets for granules of mesalazine are routinely used in the art, as evidenced by the teaching of Valducci.

One of ordinary skill in the art would find it obvious to modify or adjust the level of ethyl cellulose coating on the mesalazine granulates and test the release profile of the granulates according to the established in vitro testing protocol of the USP during the process of routine experimentation. One of ordinary skill in the art would decrease the amount of coating in order to increase the release of mesalazine from the granulate. Conversely, one of ordinary skill in the art would increase the amount of coating in order to reduce the release rate of mesalazine from the granulate. The amount of coating on the granulate is a recognized result effective variable, i.e., adjusting the amount of coating affects the release rate of the active ingredient. Halskov teaches that generally,

the release can be controlled by varying the thickness of the coating (Page 12, lines 12-19). Please see MPEP 2144.05.

Regarding instant claim 1, the limitation of a coated granulate comprising a pharmaceutically acceptable binder and from 92 to 98% by weight of mesalazine would have been obvious over the granulate comprising 5-ASA (at a calculated weight percent of 91% per granulate or at a calculated weight percent of 78% per coated granulate) and polyvinylpyrrolidone, as taught by Halskov (Page 11, lines 15-18) in view of the mesalazine dosage ranging from 100 and 3000mg, as taught by Valducci (Page 3, [0045]). One of ordinary skill in the art would modify the level of 5-ASA in the coated granulate during the process of routine experimentation based on the wide dosage range of mesalazine (100 – 3000 mg) and arrive at the recited weight percent of from 92 to 98% by weight of mesalazine unless there is evidence of criticality or unexpected results. The limitation of a coating would have been obvious over the ethylcellulose coating of the granulate, as taught by Halskov (Page 11, lines 18-23). The limitation of a sachet would have been obvious over the sachets for granules containing mesalazine, as taught by Valducci (Page 3, [0045]). The limitation of adjusting the amount of coating to the specific surface area of the granulate to achieve the specifically recited in vitro release characteristics would have been obvious over the release profile of the granulates according to the established in vitro testing protocol of the USP during the process of routine experimentation. One of ordinary skill in the art would decrease the amount of coating in order to increase the release of mesalazine from the granulate. Conversely, one of ordinary skill in the art would increase the amount of coating in order

to reduce the release rate of mesalazine from the granulate. The amount of coating on the granulate is a result effective variable, i.e., adjusting the amount of coating affects the release rate of the active ingredient. Please see MPEP 2144.05.

Regarding instant claim 7, the limitation of the amount of binder would have been obvious over the calculated amount of polyvinylpyrrolidone (25g/275g = 9%) in the granulate of 5-ASA, as taught by Halskov (Page 11, lines 15-18).

Regarding instant claim 9, the limitation of the ratio of the weight of the coating to the weight of the mesalazine would have been obvious over the calculated ratio of the amount of coating per coated granulate (EC = 45g/320g = 14.06%) and the amount of mesalazine per coated granulate (250g/320g = 78%), i.e. 14.06%: 78% or 1:5.55%, as taught by Halskov (Page 11, lines 15-23).

Regarding instant claim 10, the limitation of the pharmaceutical formulation consisting essentially of mesalazine, a pharmaceutically acceptable binder and a coating would have been obvious over the granulate of 5-ASA, polyvinylpyrrolidone, and ethylcellulose coating, as taught by Halskov (Page 11, lines 15-23).

Regarding instant claim 11, the limitation of the pharmaceutical formulation packed in a sachet would have been obvious over the sachets for granules containing mesalazine, as taught by Valducci (Page 3, [0045]).

Regarding instant claim 21, the limitation of the sachets comprising a total dosage amount of mesalazine would have been obvious over the sachets of mesalazine granules with a dosage ranging from 100 and 3000mg, as taught by Valducci (Page 3, [0045]).

Regarding instant claim 26, the limitation of the in vitro release characteristics would have been obvious over the ethylcellulose coated granulates of mesalazine and polyvinylpyrrolidone taught by Halskov (Page 11, lines 15-23) in view of the sachets comprising granulates of mesalazine taught by Valducci (Page 3, [0045]). One of ordinary skill in the art would find it obvious to test the release profile of the granulates according to the established in vitro testing protocol of the USP during the process of routine experimentation. The recited release rate of 40 – 60% of the total amount of mesalazine after 90 min, when measured in a model system using a USP Paddle System 2 operated at 37ºC with stirring at 100 rpm would have been an obvious variant based on release testing according to established USP protocol, unless there is evidence of criticality or unexpected results.

Regarding instant claim 29, the limitation of Povidone as the binder would have been obvious over the polyvinylpyrrolidone taught by Halskov (Page 11, lines 15-23).

Regarding instant claim 30, the limitation of the coating comprising ethylcellulose would have been obvious over the ethylcellulose coating taught by Halskov (Page 11, lines 15-23).

Regarding instant new claim 33, the limitation of a granulate comprising 92 to 98% by weight of mesalazine would have been obvious over the granulate comprising 5-ASA (at a calculated weight percent of **91%** per granulate, as taught by Halskov (Page 11, lines 15-18) in view of the mesalazine dosage ranging from 100 and 3000mg, as taught by Valducci (Page 3, [0045]). New claim 33 does not require a coated granulate or the 92 to 98% of mesalazine is not based on a coated granulate, rather this

percent range is based on just the granulate. One of ordinary skill in the art would modify the level of 5-ASA in the coated granulate during the process of routine experimentation based on the wide dosage range of mesalazine (100 – 3000 mg) and arrive at the recited weight percent of from 92 to 98% by weight of mesalazine unless there is evidence of criticality or unexpected results. The limitation of 2 to 8% by weight of polyvinylpyrrolidone would have been obvious over the calculated amount of polyvinylpyrrolidone (25g/275g = 9%) in the granulate of 5-ASA, as taught by Halskov (Page 11, lines 15-18). The limitation of a coating comprising a release modifying agent would have been obvious over the ethylcellulose coating taught by Halskov (Page 11, lines 15-23). The limitation of the pharmaceutical formulation packed in a sachet would have been obvious over the sachets for granules containing mesalazine, as taught by Valducci (Page 3, [0045]).

Response to Arguments

7. Applicant's arguments, see Page 8, filed 10/16/09, with respect to the rejection of claims 1, 7, 9-11, 21, 26, 29, and 30 rejected under 35 U.S.C. 103(a) as being unpatentable over Halskov (WO 81/02671) in view of Valducci (US 2002/0034541 A1) have been fully considered but are not persuasive.

Applicant argues that "in part, claim 1 now recites a coated granulate "wherein the coated granulate comprises: a pharmaceutically acceptable binder" and 92 to 98% by weight of mesalazine or a pharmaceutically acceptable salt thereof." By contrast, the Office Action admits that Halskov only discloses a coated granulate with 78% mesalazine. Therefore, amended claim 1 recites a coated granulate with a significantly

higher percent mesalazine when compared to Halskov." Applicant argues that a jump from 78% to 92% is a significant improvement. Applicant argues that neither Halskov nor Valducci independently or in combination discloses, suggests, or makes obvious an oral pharmaceutical formulation in the form of a coated granulate in a sachet, wherein the coated granulate comprises a pharmaceutically acceptable binder and from 92 to 98% by weight of mesalazine or a pharmaceutically acceptable salt thereof.

This is not persuasive because one of ordinary skill in the art would find it obvious to modify the level of mesalazine in the coated granulate taught by Halskov based on the desired dosage of the mesalazine. Moreover, the supporting reference, Valducci, teaches the dosage of mesalazine as ranging from 100mg to 3000mg. Therefore, one of ordinary skill in the art would find it obvious to modify, i.e., increase or decrease the mesalazine loading in the coated granulate to accommodate the wide dosage range of mesalazine. The amount of mesalazine loaded in the coated granulate is a result effective variable that can be manipulated by one of ordinary skill during the process of routine optimization.

Applicant disagrees with the position the Office Action takes on the first paragraph of page 7. Applicant argues that one novel aspect of the presently claimed invention is the ability to achieve specific release profiles while still maintaining a high drug load capacity.

This is not persuasive because since it would be obvious to prepare a coated granulate comprising mesalazine with a high drug loading based on the wide range of mesalazine dosages in the art (100-3000mg as evidenced by Valducci), it is also

obvious to adjust the amount of coating to the specific surface area of the granulate to achieve any desired in vitro release characteristics. One of ordinary skill in the art would find it obvious to test the release profile of the coated granulates according to the established in vitro testing protocol of the USP during the process of routine experimentation. One of ordinary skill in the art would decrease the amount of coating in order to increase the release of mesalazine from the granulate. Conversely, one of ordinary skill in the art would increase the amount of coating in order to reduce the release rate of mesalazine from the granulate. The amount of coating on the granulate is a result effective variable, i.e., adjusting the amount of coating affects the release rate of the active ingredient. Please see MPEP 2144.05.

Therefore, the rejection of 04/17/09 is maintained.

Claim Rejections - 35 USC § 103

8. Claims 6 and 27-28 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Halskov (WO 81/02671) in view of Valducci (US 2002/0034541 A1) and further in view of Augsburger et al. (US 2002/0177579 A1).

The teachings of Halskov and Valducci are stated above.

Halskov and Valducci do not expressly teach a pharmaceutical formulation having a similarity factor f_2 above 30 as compared to a standard formulation having in vitro release characteristics such that 12% of the total amount of mesalazine in the standard formulation is released after 15 minutes; 50% of the total amount of mesalazine in the standard formulation is released after 90 minutes; and 85% of the total amount of mesalazine in the standard formulation is released after 240 minutes.

Augsburger teaches an extended release granulation of a drug to achieve a specific drug release profile (Abstract). Augsburger also teaches that the similarity factor as defined by f_2 is used to determine whether two dissolution profiles are similar and that an f_2 between 50 and 100 suggests the two dissolution profiles are similar (Page 8, [0071] – [0072]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a granulate comprising 5-ASA (or mesalazine), polyvinylpyrrolidone, and coat the granulate with ethyl cellulose, as taught by Halskov, place the granules of mesalazine in sachets, as taught by Valducci, measure the in vitro release profile of the mesalazine, as established in the standard USP protocol during the process of routine experimentation, in view of the calculation of a similarity factor in order to determine whether two dissolution profiles are similar, as suggested by Augsburger, and produce the instant invention.

One of ordinary skill in the art would do this because a similarity factor is routinely used in the art to determine the similarity of two dissolution profiles, as evidenced by the teaching of Augsburger.

Regarding instant claim 6, the limitation of the similarity factor would have been obvious over the calculation of a similarity factor in order to determine whether two dissolution profiles are similar, as suggested by Augsburger (Page 8, [0071] – [0072]). The limitations of the release profile (12% of the total amount of mesalazine in the standard formulation is released after 15 minutes; 50% of the total amount of mesalazine in the standard formulation is released after 90 minutes; and 85% of the

total amount of mesalazine in the standard formulation is released after 240 minutes) would have been obvious over the release profile of the granulates according to the established in vitro testing protocol of the USP during the process of routine experimentation.

Regarding instant claims 27-28, the limitations of the similarity factor f_2 above 40 and above 50 when compared to the standard formulation would have been obvious over the teaching by Augsburger that the similarity factor as defined by f_2 is used to determine whether two dissolution profiles are similar and that an f_2 between 50 and 100 suggests the two dissolution profiles are similar (Page 8, [0071] – [0072]).

Response to Arguments

9. Applicant's arguments, see Page 9, filed 10/16/09, with respect to the rejection of claims 6 and 27-28 under 35 U.S.C. 103(a) as being unpatentable over Halskov (WO 81/02671) in view of Valducci (US 2002/0034541 A1) and further in view of Augsburger et al. (US 2002/0177579 A1) have been fully considered but are not persuasive.

Applicant argues that claims 6 and 27-28 depend from amended claim 1 and that in view of the above arguments and amendments relating to claim 1, claims 6 and 27-28 are in condition for allowance.

This is not persuasive because the deficiency in the combination of Halskov and Valducci with respect to claims 6 and 27-28 is with respect to the similarity factor. This deficiency is remedied by Augsburger and this reference is properly combined with Halskov and Valducci because similarity factor is routinely used in the art to determine the similarity of two dissolution profiles.

Therefore, the rejection of 04/17/09 is maintained.

New claim 33

10. Applicant 's arguments, see Page 9, filed 10/16/09, with respect to new claim 33 have been fully considered but are not persuasive.

Applicant argues that the cited references fail to disclose a granulate with 92 to 98% by weight of mesalazine and that the cited prior art only discloses 9% polyvinylpyrrolidone.

This is not persuasive because the recited percent ranges would have been obvious over the granulate comprising 5-ASA (at a calculated weight percent of **91%** per granulate, as taught by Halskov (Page 11, lines 15-18) in view of the mesalazine dosage ranging from 100 and 3000mg, as taught by Valducci (Page 3, [0045]). New claim 33 does not require a coated granulate. The limitation of 92 to 98% of mesalazine is not based on a coated granulate, rather this percent range is based on just the granulate. One of ordinary skill in the art would find 92% obvious over 91% and would be able to achieve this level of mesalazine in the granulate during the process of routine experimentation. Similarly, one of ordinary skill in the art would find 8% obvious over the calculated amount of polyvinylpyrrolidone (25g/275g = 9%) in the granulate of 5-ASA, as taught by Halskov (Page 11, lines 15-18). The recited weight percentages are obvious variants unless there is evidence of criticality or unexpected results.

Therefore, new claim 33 is included in the rejection over Halskov and Valducci. Since this rejection was necessitated by Applicant's amendment, this action is made FINAL.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615